EXHIBIT 50

UNITED STATES DISTRICT COURT

CENTRAL DISTRICT OF CALIFORNIA

MEDIMMUNE, INC.,

Plaintiff,

v.

GENENTECH, INC. and CITY OF HOPE,

Defendants.

Case No. CV 03-02567 MRP (CTx)

CLAIM CONSTRUCTION ORDER

I.
INTRODUCTION

Plaintiff MedImmune, Inc. ("MedImmune") is a biotechnology company whose most successful product is Synagis®, a drug used to prevent a potentially serious lower respiratory tract disease (respiratory syncytial virus, or RSV) in children. The Defendants are a biotechnology company, Genentech, Inc. ("Genentech"), and a nonprofit organization, City of Hope, who are co-assignees of the only patent-in-suit,[1] United States Patent No. 6,331,415B1 (issued on December 18, 2001) ("the '415 Patent"). Defendants maintain that Synagis® is

[1] References to Genentech in the remainder of this Order are intended to indicate both Genentech and City of Hope.

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covered by the '415 Patent and subject to royalties in accordance with the license. MedImmune paid and continues to pay these license royalties to Genentech; however, MedImmune seeks by this declaratory action to challenge the validity and enforceability of the '415 Patent. At this stage, the parties dispute the meaning of, and ask for constructions from this Court for, five (5) claim terms contained in the '415 Patent, in accordance with *Markman v. Westview Instruments, Inc.*, 517 U.S. 370 (1996).

II.
BACKGROUND

A. The Patented Technology

The '415 Patent claims a method of producing monoclonal antibodies using recombinant deoxyribonucleic acid ("DNA") technology. Synagis® is a monoclonal antibody; MedImmune licenses the '415 Patent for the production of its Synagis® product. The process of the patent involves transforming a host cell with DNA sequences that code for the polypeptide chains (the heavy and light chains) that form the Y-shaped antibody. '415 Patent, col. 28. Transformation of the host cell (typically a bacterium or yeast) is accomplished by inserting a vector or vectors (e.g. a plasmid, which may be derived from a virus) containing DNA sequences coding for the variable domains of the desired chains. *Id.* The vector or plasmid (or plasmids, if one plasmid is used to code for each chain) becomes part of the host cell's DNA sequence, and the host cell begins expressing the sequence by producing the desired protein chains. This process allows the heavy and light chains to be produced as separate molecules in a single host cell and expressed from that cell as an immunlogically functional antibody. *Id.*

B. Procedural History

Genentech and the City of Hope are the owners of United States Patent No. 4,816,567 (known as the Cabilly I Patent), filed on April 8, 1983, and the '415 Patent (known as the Cabilly II Patent), which is a continuation of Cabilly I, filed on June 10, 1988. Celltech R&D, Ltd. ("Celltech") owns United States Patent No. 4,816,397 (known as the Boss Patent), having a British priority date of March 25, 1983. In accordance with 35 U.S.C. § 135, the United States Patent and Trademark Office (PTO) declared an interference between the Boss Patent and the Cabilly II application. The PTO interference proceedings consumed seven and a half years. The Board of Patent Appeals and Interferences decided priority in favor of the senior party, Boss, holding that Cabilly had not established an actual reduction to practice before the Boss Patent's British priority date. *Cabilly v. Boss*, 55 U.S.P.Q.2d 1238 (Bd. Pat. App. & Int. 1988).

Genentech then filed a civil action pursuant to 35 U.S.C. § 146 in the Northern District of California. After various proceedings, the district court found disputed facts concerning conception and reduction to practice required trial and urged Genentech and Celltech to resolve the issue of priority with the aid of mediation. Genentech and Celltech retained a mediation service, and a retired judge served as mediator. A settlement agreement was duly reached, whereby Genentech and Celltech agreed that the Cabilly II application was entitled to priority as against the Boss patent, based in part on new evidence of the content of a draft patent application during the period leading to filing of the Genentech application. Genentech and Celltech also entered into a cross-license agreement that included a formula for sharing of royalties. Judgment was entered on the parties' resolution of the issue of priority, and the district court directed the PTO to vacate its prior decision, revoke the Boss Patent, and issue a patent on the Cabilly II

application. *See Genentech, Inc. v. Celltech R & D, Ltd.*, No. 3:98cv03929 (N.D. Cal. March 16, 2001).

Genentech and Celltech jointly presented this judgment to the PTO, with a petition requesting that the PTO cancel the Boss Patent and issue a patent on the Cabilly II application. The Board entered an order that Cabilly was the prior inventor, but did not follow the requested procedure. The Board stated that the Boss Patent was cancelled by operation of law when the district court's judgment became final and was not appealed, and that no further action by the PTO was required. The Board also observed that an Information Disclosure Statement filed by Genentech in 1991 had not been acted upon, and returned the Cabilly II application to the patent examiner for review of any "ground not involved in judicial review." Genentech then cited a large number of additional references to the examiner, and provided various documents from the record of the § 146 action. After further examination, the Cabilly II Patent was issued on December 18, 2001, eleven years after the inception of the interference.

Since 1997, MedImmune has been licensed by Genentech under the Cabilly I Patent and, by the terms of that agreement, received a license under the Cabilly II Patent. In addition, MedImmune had since 1998 been licensed by Celltech under the Boss Patent. After issuance of Cabilly II, Genentech advised MedImmune that a MedImmune product, brand name Synagis®, was covered by Cabilly II and subject to royalties in accordance with the license terms. Although MedImmune paid and continues to pay license royalties to Genentech, MedImmune has done so under protest, filing the instant declaratory judgment action in this Court requesting a determination that the Cabilly II Patent was invalid or unenforceable.

This Court, applying *Gen-Probe, Inc. v. Vysis, Inc.*, 359 F.3d 1376 (Fed. Cir. 2004), held that MedImmune, as a licensee in good standing and not in reasonable apprehension of suit,

could not bring a declaratory action to challenge a patent under which it is licensed, and dismissed the suit as non-justiciable under the Declaratory Judgment Act. The Federal Circuit affirmed, rejecting MedImmune's argument that it met the requirements of the Declaratory Judgment Act because, if it stopped paying the royalties, it could be sued. *MedImmune, Inc. v. Genentech, Inc.*, 427 F.3d 958 (Fed Cir. 2005). The Supreme Court, however, reversed, holding in *MedImmune, Inc. v. Genentech, Inc.*, 127 S.Ct. 764 (2007), that a federal district court possesses subject-matter jurisdiction under the Declaratory Judgment Act to hear a suit brought by a patent licensee against the patent's owner to establish the patent's invalidity.

On remand to this Court, litigation of this long-running patent dispute resumed.[2] The Court held a *Markman* hearing on July 11, 2007, where both parties renewed their arguments on the remaining disputed terms.[3] Neither expert nor inventor testimony was received. Currently at

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[2] MedImmune objects to the agreement between Genentech and Celltech and the resulting '415 "Cabilly II" Patent, as it allegedly created a 29-year patent monopoly over core technology essential to the artificial production of monoclonal antibodies. MedImmune complains that, while Celltech's '397 "Boss" Patent was set to expire in 2006, inducing reliance by MedImmune and other biotechnology firms in the industry on that expiration date, the '415 Patent -- which effectively replaces the '397 Patent -- will not expire until 2018. Accordingly, MedImmune has brought ten causes of action related to the '415 Patent, six of which were resolved on summary judgment. The remaining causes of action involve issues of non-infringement, invalidity, and inequitable conduct. Most relevant for claim-construction purposes are MedImmune's requests for declaratory judgment: (1) that Synagis® does not, but for the 1997 license agreement, infringe any claim of the '415 Patent; (2) that the '415 Patent is invalid as anticipated and/or obvious under the terms of the patent statute; (3) that the '415 Patent is invalid for non-statutory obviousness-type double patenting; and (4) that the '415 Patent is invalid under 35 U.S.C. §112, which lists requirements for the specification (although the Complaint does not detail how this section is violated).

[3] The parties submitted their claim construction briefs prior to remand: Genentech's OPENING BRIEF REGARDING CLAIM CONSTRUCTION was filed 12/22/2003; MedImmune's OPPOSITION BRIEF REGARDING CLAIM CONSTRUCTION was filed 01/26/2004; while Genentech's REPLY BRIEF REGARDING CLAIM CONSTRUCTION was filed 02/13/2004. On January 28, 2004, this Court issued an order requiring the parties to meet and confer to reduce the number of claims to be construed at the Markman hearing. In the parties' JOINT STATEMENT RESPONSIVE TO COURT'S JANUARY 28, 2004 ORDER RE: TERMS TO BE CONSTRUED AT *MARKMAN* HEARING ("Joint

issue before the Court are five disputed terms: (1) "produced as separate molecules in said transformed single host cell"; (2) "vector"; (3) "plasmid"; (4) "derived from"; and (5) "different insertion sites."

III.
LEGAL STANDARD

"[T]he construction of a patent, including terms of art within its claim, is exclusively within the province of the court." *Markman*, 517 U.S. at 372. "The words of a [patent] claim are generally given their ordinary and customary meaning," which is "the meaning that the term would have to a person of ordinary skill in the art in question . . . as of the [patent's] effective filing date." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312-13 (Fed. Cir. 2005) (*en banc*). In interpreting a claim, "the court should first look to the intrinsic evidence of record, i.e. the patent itself, including the claims, the specification, and if in evidence, the prosecution history." *Veronicas Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996). The patent specification, in particular, is central to a determination of "the meaning of a claim term as it is used by the inventor in the context of the entirety of his invention." *Comark Commc'ns v. Harris Corp.*, 156 F.3d 1182, 1187 (Fed. Cir. 1998). The patent specification "is always highly relevant to the claim construction analysis. Usually it is dispositive; it is the single best guide to the meaning of a disputed term." *Phillips*, 415 F.3d at 1315 (quoting *Vitronics*, 90 F.3d at 1582). "The construction that stays true to the claim language and most naturally aligns with the patent's description of the invention [in the specification] will be, in the end, the correct

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Statement"), filed 2/9/2004, the parties agreed on definitions for two and agreed not to seek resolution for three formally disputed terms. At that point, only six terms remained for the Court to construe. At the July 11, 2007 *Markman* hearing, the parties informed the Court that they had reached consensus on yet one additional term: "variable domain of the immunoglobulin."

construction." *Id.* at 1316 (quoting *Renishaw PLC v. Marposs Societa' Per Azioni*, 158 F.3d 1243, 1250 (Fed. Cir. 1998)). Although a patent claim may at times contain terms that do not appear in the specification, all "terms and phrases used in the claims must find clear support or antecedent basis in the [specification] so that the meaning of the terms in the claims may be ascertainable by reference to the [specification]." *Tandon Corp. v. U.S. Int'l Trade Comm'n*, 831 F. 2d 1017, 1024 (Fed. Cir. 1987); *see also Lockwood v Am. Airlines, Inc.*, 107 F.3d 1565, 1572 (Fed. Cir. 1997).

IV.
CLAIM CONSTRUCTION

A. Undisputed Claim Terms

The parties have agreed to the construction of the following claims terms, clauses or phrases shown in the table below. The Court therefore preliminarily accepts the following constructions:

Claim Term	*Agreed Construction*
"immunoglobulin"	"a tetrameric molecule consisting of two relatively long polypeptide chains called heavy chains and two shorter polypeptide chains called light chain, or aggregates of such tetrameric molecules, whether or not specific immunoreactive activity is a property"
"immunologically functional immunoglobulin fragment"	"a portion of an immunoglobulin that is capable of selectively binding to a particular antigen or antigen family"
"transforming" [said single host cell]	"altering the DNA of a cell by the inclusion of foreign DNA"
"transformed" [host cell] and [host cell] "transformed"	"a cell whose DNA includes foreign DNA; the term includes the progeny of the initially transformed host cell"
"species"	"a species consists of related organisms capable of interbreeding"
"class"	"'class' refers to one of the five types of heavy chains that may be contained within an immunoglobulin: gamma, mu, alpha, delta, or epsilon"

"monoclonal antibody producing hybridoma"	"a hybrid cell, created by fusing a B cell with an immortal cell; the resulting hybridoma is both immortal and capable of producing the genetically encoded monoclonal antibody of the B cell"
"variable domain of the immunoglobulin"	"the N-terminal end of the heavy of the heavy and light chains up to the beginning of the constant domain"
"independently expressing"	[*No construction necessary*]
"secreted therefrom as an immunologically functional immunoglobulin fragment"	[*No construction necessary*]
"same source"	[*No construction necessary*]

B. Disputed Claim Terms

The parties disagree on the construction of the following claim terms, clauses or phrases as shown in the table below:

Claim Term	*Claims*	*Genentech's Proposed Construction*	*MedImmune's Proposed Construction*
"produced as separate molecules in said transformed single host cell"	1(ii)	[*a self-defining term requiring no further construction*]	"the heavy and light chains are separate molecules while in the single host cell"
"vector"	2, 3, 4, 15, 16, 17, 18, 21(b)	"a DNA construct used to alter the DNA of a host cell to include foreign DNA. The term "vector" includes an "expression vector," as defined in column 8 of the patent"	"a separate DNA molecule that transfers a DNA segment into a host cell"
"plasmid"	4, 5, 16	"an autonomous, self-replicating extrachromosomal (usually circular) DNA sequence that corresponds thereto"	"an autonomous, self-replicating extrachromosomal circular DNA molecule"

"derived from"	12, 13, 14	to be based on, in whole or in part	"obtained from"
"different insertion sites"	15	"in the vector, the DNA sequence encoding for at least the variable domain of the heavy chain is not contiguous to the DNA sequence encoding for at least the variable domain of the light chain"	"separate, not contiguous restriction sites of the vector"

1. "Produced As Separate Molecules In Said Transformed Single Host Cell"

The disputed term is used in claim 1 of the '415 Patent, and in the claims that depend from it. Claim 1 describes a two-step process for producing an immunoglobulin molecule or fragment. '415 Patent, col. 28, ll. 46-49. The second of these steps provides for:

> independently expressing said first DNA sequence and said second DNA sequence so that said immunoglobulin heavy and light chains are *produced as separate molecules in said transformed single host cell.*

'415 Patent, col. 28, ll. 46-49 (emphasis added).

The parties have now agreed that the prefatory phrase – "independently expressing said first DNA sequence and said second DNA sequence" – needs no further construction. The substance of the parties' remaining dispute is whether the chains must remain separate until they are outside the host cell, or whether they may combine while still inside. MedImmune proposes a construction that requires the heavy and light chains to exist as separate molecules for however long they remain in and until they exit the host cell. MedImmune urges the Court to remain cognizant of the '415 Patent's unique drafting history while considering its construction. Specifically, it points out that Genentech did not draft the claims of the '415 Patent. Rather, they

were drafted by the Boss patentees and purportedly supported by the Boss Patent's specification. Genentech has acknowledged copying the Boss patent's claims verbatim to provoke an interference, and the result has been a chimera: the '415 (Cabilly II) specification appended to the '397 (Boss) claims.

It is in the context of this union that MedImmune urges this Court not to construe the claims of the '415 Patent broadly enough to encompass the synthesis of an immunoglobulin molecule -- i.e., the *assembly* of the heavy and light chains -- within a single host cell. After all, MedImmune observes, Genentech never produced immunoglobulins within a host cell; the '415 specification does not teach and arguably admits to ignorance[4] of a technique for doing so; and Dr. Cabilly was focused on an entirely different method according to which well-known *in vitro* recovery and purification techniques would enable assembly of the chains outside the cell. Indeed, Dr. Cabilly extolled the virtues of external assembly, writing that "[t]he ability of the method of the invention to produce heavy and light chains or portions thereof, *in isolation from each other* offers the opportunity to obtain *unique and unprecedented assemblies*...." '415 Patent, col. 12, ll. 58-63 (emphasis added).

Genentech disagrees with MedImmune's proposed construction because it contradicts the plain language of claim 9 of the '415 Patent. Claim 9 provides for "[a] process according to claim 1 wherein the immunoglobulin heavy and light chains are expressed in the host cell and

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[4] The '415 Patent specification provides that "[w]hen heavy and light chain are coexpressed in the same host, the isolation procedure is designed so as to recover reconstituted antibody . . . [which] . . . can be accomplished in vitro as described below, *or might be possible in vivo in a microorganism which secretes the IgG chains out of the reducing environment of the cytoplasm.* '415 Patent, col. 12, ll. 50-55 (emphasis added). Dr. Cabilly's speculation that *in vivo* assembly "might be possible" in yeast can reasonably be construed as an admission that techniques sufficient to induce *in vivo* assembly were unknown to him – or, at a minimum, not taught by the '415 Patent – especially with respect to mammalian cells.

secreted therefrom as an immunologically functional immunoglobulin molecule or immunoglobulin fragment." '415 Patent, col. 28, ll. 64-67. The plain language of this claim implies that the drafter contemplated that the chains produced as separate molecules according to claim 1 would combine prior to being secreted: the chains are "expressed" (i.e., independently, per claim 1); "secreted therefrom" (i.e., expelled out of the host); secreted "as" (i.e., in a state or structure not yet identified); and secreted in the form of "immunologically functional" units (i.e., whose functionality depends on the heavy and light chains combining). MedImmune's proposed construction effectively rewrites claim 9 to require that the heavy and light chains only combine into immunologically functional molecules after their secretion from the host cell. Genentech argues such a revision renders claim 9 "nonsensical" and claim 10 superfluous. Claim 10 provides for "[a] process according to claim 1 wherein the immunoglobulin heavy and light chains are produced in insoluble form and are solubilized and allowed to refold in solution to form an immunologically functional immunoglobulin molecule or immunoglobulin fragment." Col. 29, ll. 1-5. If the Court were to accept MedImmune's proposed construction, claims 9 and 10 would be indistinguishable, each anticipating secretion of the heavy and light chains *before* combination into immunologically functional molecules.

Genentech argues that the doctrine of claim differentiation prohibits that result. The Court must presume that claims 9 and 10 of the '415 Patent each have a different scope, *see Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1325-26 (Fed. Cir. 2003), and reject proposed constructions that would render either claim superfluous, *see Tandon Corp. v. U.S. Int'l Trade Comm'n*, 831 F.2d 1017, 1023 (Fed. Cir. 1987). In reply, MedImmune observes that the Court is equally bound under *Phillips* to construe claim 1 "in view of the ['415 Patent's] specification, of which [it is] a part." 415 F.3d at 1321. The *Phillips* court emphasized the

importance of the specification in claim construction, calling it "the single best guide to the meaning of . . . disputed term[s]" and "[u]sually . . . dispositive." *Id.* MedImmune acknowledges that claims 9 and 10 favor Genentech, but submits that the '415 specification, as well as the language of claim 1 itself, "overwhelmingly" favors MedImmune. *Markman* Hr'g Tr. 43:18-20.

This tension between the claims of the '415 Patent and the '415 Patent's specification is not surprising given the '415 Patent's drafting history. A specification written by Dr. Cabilly, whose research involved bacteria, has been combined with claim language written by Dr. Boss, whose research involved yeast. Dr. Cabilly appears to have used plasmid vectors that did not become integrated into the host cell's genome to transform bacterial cells from which heavy and light chains could be retrieved by lysis for subsequent *in vitro* assembly. Dr. Boss also appears to have used vectors that did not become integrated into the host cell's genome, but he did so for the purpose of transforming yeast cells which, once transformed, will assemble the heavy and light chains into antibodies *inside* the cell.

Dr. Boss' experience with *in vivo* assembly in yeast may explain the genesis of and rationale for claim 9 in a patent whose named inventor, Dr. Cabilly, merely theorized (and that only in passing) about the feasibility of the very invention which claim 9 purports to encompass. It also exposes the futility in attempting to ascertain "what the inventors actually invented and intended to envelope with the claim." *Phillips*, 415 F.3d at 1316. *Phillips* directs the Court to construe the '415 Patent's claims in light of its specification as if they were the product of one mind, and yet there appears not to have been one "true intent" behind this patent for the Court to discern and use as its touchstone. *Id.*

MedImmune's solution to this interpretive dilemma is pragmatic. They cite *Saunders v. Comfortrac*, No. 2006-1576, 2007 WL 1827843 (Fed. Cir. 2007), for the proposition that conflicts between patents' claims and their specifications which give rise to conflicting inferences and threaten to trigger anomalous claim constructions should be weighed and balanced by courts to ensure proper constructions. MedImmune's position is, essentially, that the Court should adopt its proposed construction because its proposed construction is more faithful and does less violence to the claims than Genentech's proposed construction is and does to the specification. The Court is sympathetic to the realism urged by MedImmune's approach, but resorting, here, to the lesser of two evils does not seem to be the correct solution.

On its face, the plain and ordinary meaning of the disputed phrase, "produced as separate molecules in said transformed single host cell," does not permit the Court to reach MedImmune's proposed construction. The language of claim 1(ii) is unambiguous in its silence about the fate of the immunoglobulin heavy and immunoglobulin light chains after their independent expression according to claim 1(i). The term "produced" clearly refers to "created" or "manufactured." These words define a singular event in time. Claim 1(ii) requires that the heavy and light chains be separately "created" or "manufactured," but it is agnostic as to what may or must happen afterwards. Revising "produced" to read "produced and maintained," as MedImmune proposes, or "initially produced," as Genentech suggests, would be to enlarge rather than clarify the meaning of the term.

Similarly, the term "as" defines the form, structure, or status of that which is produced at the moment of its production. The heavy and light chains are produced "as" separate molecules. However, the term does not speak to the issue of whether or for how long they remain that way. Finally, the term "in" refers to the location in space where production occurs, at the moment in

time when it does. "In" means simply "within" or "inside" the cytoplasm of, and "not outside" the outermost boundary defining the "transformed single host cell" as such.

Thus, claim 1(ii) provides only that the transformed single host cell give rise, within the boundaries of its cell membrane, to two, separate and distinct molecules: the heavy chain and the light chain. Whether the heavy and light chains must remain separated after their creation as distinct molecules in, but prior to their recovery or secretion from, the host cell is not addressed by the text. Claims 9 and 10 fill in that gap, describing scenarios where the chains would fold inside the host cell so that a functional molecule or fragment is released (claim 9), and those where the chains fold only after being recovered, purified, and induced to do so *in vitro*. '415 Patent, cols. 28-29.

In the future, this Court may be called to determine whether assembly within the host cell was adequately described in the specification; however, neither that enterprise nor its likely outcome is required as a part of claim construction. Accordingly, the Court concludes that the term from claim 1(ii), "produced as separate molecules in said transformed single host cell," is clear on its face. It requires that something be created, describes the form of that thing at the moment of its creation, and specifies where creation must occur at the moment at which it does. The language requires nothing more, and the Court offers no further construction.

2. "Vector"

The term vector is used widely throughout the '415 Patent, and it appears in asserted claims 2, 3, 4, 15, 16, 17, 18, and 21(b). The parties agree that for the purposes of the '415 Patent, a vector is made of DNA and is used in the process of altering a host cell. The essence of the dispute is whether a vector remains a vector after it transfers a DNA segment to and becomes

integrated in the host cell. Put differently, does a vector, as defined for the purposes of this patent, retain all necessary elements of that definition after integration into the host cell genome? Genentech argues that the claims of the '415 Patent clearly indicate that a vector does not cease to be a vector merely because it becomes integrated within the chromosomal DNA of the transformed host cell. Genentech observes that claim 18 recites "a transformed host cell comprising at least two vectors." The term "vector" itself is not defined in the specification; however, Genentech argues its usage in the specification also strongly suggests the survival of vectors qua vectors post integration. At column 10, lines 19-25 of the Patent, the specification discusses the provision of an origin of replication by vector integration, commenting that "[i]f the vector is integrated in into the host cell chromosome, the latter is often sufficient [for replication]." Genentech also appeals to the specification to incorporate the meaning of the undisputed term, "expression vector," as it is defined at column 8, lines 3-25 of the Patent, into the meaning of the disputed term, "vector." The specification teaches that

> "Expression vector" includes vectors which are capable of expressing DNA sequences contained therein, i.e., the coding sequences are operably linked to other sequences capable of effecting their expression. It is implied, although not always explicitly stated, that these expression vectors must be replicable in the host organisms either as episomes or as an integral part of the chromosomal DNA. Clearly a lack of replicability would render them effectively inoperable. A useful, but not a necessary, element of an effective expression vector is a marker encoding sequence--i.e. a sequence encoding a protein which results in a phenotypic property (e.g. tetracycline resistance) of the cells containing the protein which permits those cells to be readily identified. In sum, "" expression vector" is given a functional definition, and any DNA sequence which is capable of effecting expression of a specified contained DNA code is included in this term, as it is applied to the specified sequence.

Genentech relies on this language to equate vectors with expression vectors. At the *Markman* hearing, Genentech's counsel argued that, because "[a]n expression vector is used in the patent to define a particular type of vector that is used to put in DNA for the purposes of

expressing that DNA . . . as a practical matter, the vectors that are being used in connection with this invention are, one would think, expression vectors." Indeed, according to Genentech's counsel, the "patentees were *explicit* that, when they used the term vector, they meant that portion of the DNA that was being used to effect the expression of the DNA sequence, regardless of whether it had been integrated into the chromosomal DNA or not" (emphasis added).

Yet, Genentech's proposed construction suffers from a critical flaw. Genentech is no doubt correct: expression vector is a type of vector. The patentees were anything but explicit, however, regarding their intended effect of the former on our understanding of the latter. Merely characterizing "expression vector" as a subset of "vector," as Genentech attempts to do, cannot establish an equivalence between the two terms. Subsets necessarily are narrower than the sets from which they are drawn. Knowing the defining properties of a subset, here "expression vector," simply is not probative of the properties of the parent set, here "vector." The elements of the definition of "expression vector" set forth in the specification must necessarily include elements common to vector, which define the class, just as they must include elements that vector omits, so as to distinguish the subclass. Because those points of commonality are impossible to identify absent an independent definition of "vector," the utility of the patent's definition of "expression vector" for the Court's construction of "vector" is limited.

In sum, "expression vector" cannot simultaneously be coextensive with and a subclass of "vector." Likewise, the patentees did not explicitly equate the two; an equivalence cannot be implicitly drawn based on the mere existence of a species-genus relationship; and, without more, features of the genus cannot be deduced from features of the species. Even if the patentee had intended to equate "expression vector" with "vector," Genentech itself would refuse to accept the patent's definition of the former as sufficiently descriptive of the later. This is because

"expression vector" is entirely silent on the transformational qualities of "vector," the importance of which neither party disputes.

As defined by the specification, an "expression vector" need be nothing more than "any DNA sequence which is capable of effecting expression of a specified contained DNA code," however (and whenever) that sequence came to be located where it is. Literally read, this definition would encompass all genes, which is to say, any genetic sequence that directly codes for protein would count as a vector.[5] The fact that Dr. Cabilly transformed host cells using vectors that did not become integrated into the host cell's chromosome may explain how "expression vector" came to receive such an expansive definition. What the definition fails to encompass, however, is any role for vectors as transformational agents.

Yet, the capacity for altering DNA is at the core of what it is to be a "vector." Although Genentech accuses MedImmune of exclusive reliance on a dictionary definition, a person of ordinary skill in the field of molecular biology would indeed understand the term vector to mean a DNA molecule that transfers a DNA segment into a host cell. *See, e.g.,* King, A Dictionary of Genetics, 3d ed. at 410 (Witham Decl. Ex. F) (defining "vector" as "a self-replicating DNA molecule that transfers a DNA segment between host cells; also called a 'vehicle'"). There is no evidence that the patentees intended to abandon this functional essence of the term.

This is evident from the claims themselves. Claim 17, for example, claims "[a] host cell transformed with a vector according to claim 15." It is separately confirmed by the specification: e.g., the Abstract refers to "cells transformed with [] vectors"; the Summary Of Invention refers to "host cells and cell cultures which result from transformation with [] vectors"; and the

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[5] These stand in contrast to non-coding sequences or sequences that perform purely regulatory functions.

Detailed Description defines "[r]ecombinant host cells" as "cells which have been transformed with vectors...." Most important, Genentech itself understands "vector" this way: Genentech requests this Court to augment the patent's definition of "expression vector" so as to state a transformational role, namely its "use[] to alter the DNA of a host cell to include foreign DNA."

Thus, in order to incorporate transformational utility into the definition of "vector," Genentech must now eschew the equivalence of "expression vector" and "vector" for which it argued when the status of vector *sequence* was at stake. It is obvious that Genentech cannot have it both ways. Either the capacity to alter the DNA of a host cell is a necessary element of the definition of "vector," or it is not. If transformational agency is essential, the identity of a vector as a vector may be lost if, upon transformation, integration into the host cell chromosome removes further ability to alter DNA.

That the integrated DNA can be identified post transfer as vector sequence within the host genome is of no moment. While such DNA sequences might be traceable to -- and even, for the sake of expediency or economy of language, sometimes referred to as -- vectors, they would not themselves *be* vectors under the patent, unless they retained their transformative ability.[6] To illustrate, if the Escherichia coli genome is used as a vector and is subsequently integrated into the host cell genome, the E. coli bacterial DNA would continue as a part of the host cell chromosomal DNA, but one would not say that the E. Coli itself continued separately to exist, or that the E. Coli retained its prior distinct identity.

If, on the other hand, any coding sequence is eligible to be a vector, as Genentech maintains, transformational qualities need play no part in the construction. That counterintuitive

[6] This, of course, could happen: in bacteria, for example, vectors are not integrated, and their capacity to alter DNA is not lost; thus, their status as vectors under the patent would not change.

result would be inconsistent with both the intrinsic and extrinsic evidence. Moreover, the common presence of transformational abilities in the proposed constructions of both parties demonstrates that some transformational quality of vectors must either comprise or contribute to the Court's construction. Accordingly, the Court's construction of "vector" is "a separate DNA molecule that transfers a DNA segment into a host cell."

3. "Plasmid"

The term "plasmid" is used widely throughout the '415 Patent, appearing in claims 4, 5, and 16. The disputes over plasmid closely mirror those concerning the term "vector." MedImmune's proposed construction requires that a plasmid be and at all times remain a separate, circular molecule. MedImmune would exclude from the definition of "plasmid" a plasmid that has been integrated into the host cell's DNA. Additionally, MedImmune's proposed inclusion of the word "circular" in the construction seeks to exclude from the definition of "plasmid" a plasmid that has been "linearized" prior to its introduction into the host cell.

In contrast, Genentech argues that the specification expressly contemplates and the claims logically require that a plasmid remain a plasmid after it has been incorporated into the chromosomal DNA of the host cell. Furthermore, Genentech argues that MedImmune can point to nothing in the patent limiting the plasmids claimed to circular plasmids. Indeed, Genentech maintains that the term "plasmid" is given a functional definition by the patent not dependent on or constrained by conformation; and that, so defined, it broadly encompasses circular plasmids, circular plasmids that have been cleaved, and circular plasmids linearized by their integration into the host cell genome.

According to Genentech, the structure of the claims makes clear that a plasmid is a subset of vectors: e.g., claim 3, which depends from claim 1, provides that the "first and second DNA sequences are present in a single vector," and claim 4, which depends from claim 3, provides for a "process . . . wherein the vector is a plasmid." Claim 16 provides for "[a] vector according to claim 15 which is a plasmid." Meanwhile, the specification observes that "vectors are frequently in the form of plasmids, thus, 'plasmid' and 'expression vector' are often used interchangeably." '415 Patent, col. 8, ll. 20-23.

Because "plasmid" is understood by the Patent variously as a subset of vector and a synonym of expression vector, and because Genentech views the specification's definition of "expression vector" as encompassing "vector," Genentech maintains that "plasmid" benefits from the same. As a result, Genentech's arguments for the survival of vectors qua vectors after integration into the host cell may apply with equal force to its position that plasmids retain their identity as plasmids after integration. The flaws in these arguments apply with equal force, as well, although neither warrants detailed repetition, here. Under the patent, where a plasmid is a vector, its capacity to alter the DNA of a host cell must be preserved in order for it to retain its identity as a plasmid, which is to say, to be a plasmid-that-is-a-vector, or vector plasmid.

In contrast, where a plasmid is an expression vector, the Court first appeals to the specification's definition of expression vector. This is only a starting point, however, for two reasons: First, "plasmid" and "expression vector" are said to be used interchangeably often, but not always. Second, the "functional definition" accorded to "expression vector" is exceptionally broad. "[A]ny DNA sequence which is capable of effecting expression of a specified contained DNA code" is eligible to be a plasmid. Yet, this definition fails adequately to capture features of plasmids which are suggested in the patent and which would be readily apparent to persons of

ordinary skill in molecular biology. For example, the Detailed Description section employs the term, "expression plasmid," which the definition of "expression vector" cannot differentiate; Figures 6 and 7 disclose plasmids which are exclusively circular, while the definition of "expression vector" is silent as to shape; and the specification explicitly cites to an application that describes plasmids of the alleged invention of the '415 Patent as "non-chromosomal loop[s] of double-stranded DNA found in bacteria and other microbes, oftentimes in multiple copies per cell." *See* '415 Patent, col. 12, ll. 1-16 (citing U.S. Patent Application Ser. Nos. 307,473; 291,892; and 305, 657 (EPO Publ. Nos. 0036776; 0048970 and 0051873)).

Moreover, the plain and ordinary meaning of "plasmid" from the viewpoint of a person of ordinary skill in the art would approximate MedImmune's construction: i.e., an autonomous, self-replicating extrachromosomal circular DNA molecule. *See, e.g*, King, A Dictionary of Genetics, 3d ed. at 301 (defining plasmid as an "extrachromosomal genetic element found in a variety of bacterial species . . .[which are] . . . double stranded, closed [i.e., circular] DNA molecules"). MedImmune's construction is also consistent with the way "plasmid" has been construed by the Federal Circuit in connection with other Genentech patents. For example, in *Genentech, Inc. v. Amgen, Inc.*, 289 F.3d 761, 765 (Fed. Cir. 2002), the Federal Circuit defined a "plasmid" as "a circular piece of non-chromosomal double-stranded DNA." Thus, this Court finds that circularity and extrachromosomal situs are defining elements of the plain and ordinary meaning of "plasmid."

Genentech is correct that the concept of linearized plasmids was known in the art. However, the '415 Patent neither discloses any such linearized plasmids, nor does Genentech's appeal to the specification's reference to cleaved vectors being used as components trigger an expansion of plasmid's plain and ordinary meaning. Genentech's remedy for this deficiency, its

proposed definition of plasmids as "usually circular," fails for indefiniteness. The qualifier, "usually," essentially reads shape out of the construction; both circular and linear forms would be sufficient, but neither necessary. Genentech's reliance on its proposed language, "or the DNA sequence that corresponds thereto," threatens the same effect. Plasmids evolved in nature as (1) circular DNA molecules (2) separate from the chromosomal DNA and (3) capable of autonomous replication. Collectively, those elements capture the essential nature of a plasmid. But Genentech's construction would dispense with all three. On Genentech's account, neither extrachromosomal situs, autonomous replication, nor circularity would be necessary to find a plasmid, although collectively they would be sufficient. Accordingly, the construction of "plasmid" is "an autonomous, self-replicating extrachromosomal circular DNA molecule."

4. "Derived From"

The term "derived from" appears in claim 12, which provides for a process "wherein the constant domain is derived from the same source as the variable domain to which it is attached"; in claim 13, which provides for a process "wherein the constant domain is derived from a species or class different from that from which the variable domain to which it is attached is derived"; and claim 14, which provides for a process " wherein said first and second DNA sequences are derived from one or more monoclonal antibody producing hybridomas." The term is used in the specification of the '415 Patent, but it is not clearly defined therein. In addition, "derived from" does not appear to have been a term of art in the field of molecular biology in 1983. Thus, the parties agree that "derived from" should be given its plain and ordinary meaning. *See, e.g., Inverness Medical Switzerland GmbH v. Warner Lambert Co.*, 309 F.3d 1373, 1378 (Fed. Cir. 2002).

The parties disagree, however, on what the plain and ordinary meaning is. MedImmune cites the American Heritage Dictionary for the proposition that "derived from" means "to obtain from." Second College Ed. at 384. Genentech cites the 1976 Webster's Third New International Dictionary for the proposition that "derive" meant "to be descended or formed from (all were probably *derived* from the same ancestral stock): be derivative of."

In the abstract, this dispute addresses whether, without more, "derived from" implies origination from a single source, origination from multiple sources, origination from sources responsible for a majority contribution, origination from sources responsible for a *de minimus* contribution, or some other formulation. In practice, this dispute has implications for potential infringement. MedImmune's Synagis® product contains a variable domain originating from both a human and a murine source. Claim 12 appears to contemplate a variable domain drawn from a human source. Claim 13 appears to contemplate a variable domain drawn from a non-human source. Thus, the Court's construction of "derived from" will influence whether MedImmune potentially infringes both claims 12 and 13, or neither one.

Isolated from the context of the claims, the plain and ordinary meaning of "derived from" neither implies MedImmune's claimed limitation (i.e., restriction of origination to a single source) nor authorizes Genentech's claimed expansion (i.e., inclusion of either origination from single or multiple sources). "Derived from" simply is silent as to the nature of the direct object (i.e., the source or sources) from which the subject of the derivation originates. Accordingly, the Court is unable to construe "derived from" further; the commonplace term carries its plain and ordinary meaning.[7]

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[7] However, full consideration in context with the claims would alter this result. If the Court were to construe the expanded, technical phrase from claim 12, which reads, "derived from the same source as the variable domain," the Court's construction of this longer term would be,

5. "Different Insertion Sites"

Claims 15, 16, and 17 of the patent refer to a vector in which a first DNA sequence and a second DNA sequence are located at "different insertion sites." The dispute regarding this term concerns whether the term, "different insertion sites," refers to the ultimate locations of the two encoding DNA sequences on the vector, as Genentech claims, or the process by which the claimed vector is constructed, as MedImmune asserts. Genentech defines an "insertion site" simply as the physical location where each encoding DNA sequence, or insert, is located in the vector for inclusion in the host cell. The parties agree that "different" in the context of the claims simply implies that the two encoding DNA sequences are contiguous, which is to say that there is non-coding DNA between the two sequences that enables independent expression. MedImmune's proposed definition requires that the two encoding DNA sequences be inserted separately at two different locations on the vectors. As MedImmune's earlier proposed construction reveals, these so-called locations could only represent different restriction sites.

MedImmune is correct that Genentech's construction renders the term "insertion" superfluous. MedImmune's counsel may also have been correct when he asserted at the *Markman* hearing that Drs. Boss and Cabilly each understood the term "insertion" to mean, not

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"originating from a single source, from which the variable domain also originates." Similarly, if the Court were to construe the expanded, technical phrase from claim 13, which reads, "derived from a species or class different from that from which the variable domain to which it is attached is derived," the Court's construction of this longer term would be, "originating from a single source, different from that which the variable domain also originates." Finally, if the Court were to construe the expanded, technical phrase from claim 14, which reads, "derived from one or more monoclonal antibody producing hybridomas," the Court's construction of this longer term would be, "originating from either a single source or multiple sources." Such a construction would differentiate claims 12 and 13 from claim 14, recognize the singular articles "the" and "a" in claims 12 and 13, respectively, and vindicate the probable intent of Dr. Boss in drafting claims 12 and 13, which was to claim a process in which either the constant and variable domains each originate from one organism or each originate from different organisms.

an encoding DNA sequence, but an act -- one involving physically shearing the vector. Nevertheless, claims 15 through 17 are product claims that do not contain process limitations. As such, the process by which the vector is prepared is irrelevant; only the final position of the DNA sequences encoding for the heavy and light chains matters. *3M Innovative Properties Co. v. Avery Dennison Corp.*, 350 F.3d 1365, 1371 (Fed. Cir. 2003) ("even words of limitation that can connote with equal force a structure characteristic of the product or a process of manufacture are commonly and by default interpreted in their structural sense, unless the patentee has demonstrated otherwise"); *Vanguard Prods. Corp. v. Parker Hannifn Corp.*, 234 F.3d 1370, 1372 (Fed. Cir. 2000) ("[a] novel product that meets the criteria of patentability is not limited to the process by which it was made"); *Application of Pilkington*, 411 F.2d 1345, 1348 (C.C.P.A., 1969) (holding method of production irrelevant to a product claim's patentability). Even if MedImmune's suspicions that "insertion site" in fact denoted "restriction site" were accurate, the claims require only that the two DNA sequences be located at different sites in the end. In the context of the claim, the parties appear to agree that "different" simply means that the two encoding DNA sequence are not contiguous. The claim language is satisfied so long as the sequences of interest are separated by sufficient non-coding DNA to effect independent expression of the heavy and light chains.

The '415 Patent specification supports Genentech's construction. Although MedImmune's proposed construction no longer contains the term, "restriction sites," MedImmune's new language, "sites . . . into which DNA sequences are inserted," can be understood to refer only to the former. To accomplish, as MedImmune proposes, two separate acts of insertion resulting in, as the claims demand, the placement of the encoding DNA inserts at different locations, at least two DNA sequences recognized by restriction enzymes that then

can cut the DNA strand must be used. However, the specification uses the term "restriction site" to describe the site where a DNA sequence is added to the vector. *See* '415 Patent, col. 26, ll. 11-30 (describing Fig. 11). The term "insertion site" does not appear to be used in the patent, except in the disputed claim; however, the term "insert," sometimes referred to as the "heterologous gene insert," is used repeatedly to describe the foreign DNA sequences that will be expressed as the heavy and light chains of the antibody. *See, e.g.*, *id.*, col. 4, ll. 17-25; *id.*, col 17, ll. 23-24; *id.*, col. 18, ll. 39-47; *id.*, col. 20, ll. 13-16. In Genentech's words, the insert simply represents "the genetic payload" that will be expressed once integrated within the host cell. Reply at 19; *see* '415 Patent, col. 4, 19-20; *id.*, col. 17, ll. 23-24; *id.* col. 18, ll. 39-47; *id.*, col. 20, ll. 13-16. Considering this use of "insert" in the specification, and that the term "located" appears in claim 15, the Court finds it plausible that "insertion site" was intended to refer to the site where the insert was to be located, rather than specifically or exclusively to a restriction site.

The Court finds additional intrinsic evidence supportive of Genentech's construction in the prosecution history of the '415 Patent. Dr. Paul Cater, a former Genentech scientist, submitted a declaration in the interference explaining that inserting the gene for one chain into a vector carrying the other gene would result in two encoding DNA sequences at two distinct locations in the final vector, even thought the vector was cleaved only once. *See* Declaration of Paul Carter (June 20, 1991), at 8. He clarified that claim 15 "requires that the heavy and light chains be lodged at separate locations, or insertion sites, in the vector." *Id.*

As Genentech observed at the *Markman* hearing, "the point of the invention in many ways" is "independent expression of the heavy and light chain genes." Placing the heavy and light chain genes immediately adjacent to each other on the vector would not allow for independent expression, regardless of the number of "cuts" made in the placement process. In

that case, the heavy and light chains would be expressed together as a single strand of protein. The purpose of claim 15's call for "different insertion sites" tracks the purpose of the patent as a whole, as articulated by Genentech: to effect independent expression. It is likely the inventors would have been indifferent to the number of times the vector was cleaved provided the resulting heavy and light chains were separate and distinct. Accordingly, the Court's construction of "different insertion sites" is as follows: "in the vector, the DNA sequence encoding for at least the variable domain of the heavy chain is not contiguous to the DNA sequence encoding for at least the variable domain of the light chain, the former being separated from the later by sufficient DNA sequence to ensure independent expression."

IT IS SO ORDERED.

DATED: August 16, 2007

Mariana R. Pfaelzer
Hon. Mariana R. Pfaelzer
United States District Judge